beta2-microglobulin is a systemic pro-aging factor that impairs cognitive function and neurogenesis.

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Public Summary:
Aging drives cognitive and regenerative impairments in the adult brain, increasing susceptibility to neurodegenerative disorders in healthy individuals. Experiments using heterochronic parabiosis, in which the circulatory systems of young and old animals are joined, indicate that circulating pro-aging factors in old blood drive aging phenotypes in the brain. Here we identify beta2-microglobulin (B2M), a component of major histocompatibility complex class 1 (MHC I) molecules, as a circulating factor that negatively regulates cognitive and regenerative function in the adult hippocampus in an age-dependent manner. B2M is elevated in the blood of aging humans and mice, and it is increased within the hippocampus of aged mice and young heterochronic parabionts. Exogenous B2M injected systemically, or locally in the hippocampus, impairs hippocampal-dependent cognitive function and neurogenesis in young mice. The negative effects of B2M and heterochronic parabiosis are, in part, mitigated in the hippocampus of young transporter associated with antigen processing 1 (Tap1)-deficient mice with reduced cell surface expression of MHC I. The absence of endogenous B2M expression abrogates age-related cognitive decline and enhances neurogenesis in aged mice. Our data indicate that systemic B2M accumulation in aging blood promotes age-related cognitive dysfunction and impairs neurogenesis, in part via MHC I, suggesting that B2M may be targeted therapeutically in old age.

Scientific Abstract:
Aging drives cognitive and regenerative impairments in the adult brain, increasing susceptibility to neurodegenerative disorders in healthy individuals. Experiments using heterochronic parabiosis, in which the circulatory systems of young and old animals are joined, indicate that circulating pro-aging factors in old blood drive aging phenotypes in the brain. Here we identify beta2-microglobulin (B2M), a component of major histocompatibility complex class 1 (MHC I) molecules, as a circulating factor that negatively regulates cognitive and regenerative function in the adult hippocampus in an age-dependent manner. B2M is elevated in the blood of aging humans and mice, and it is increased within the hippocampus of aged mice and young heterochronic parabionts. Exogenous B2M injected systemically, or locally in the hippocampus, impairs hippocampal-dependent cognitive function and neurogenesis in young mice. The negative effects of B2M and heterochronic parabiosis are, in part, mitigated in the hippocampus of young transporter associated with antigen processing 1 (Tap1)-deficient mice with reduced cell surface expression of MHC I. The absence of endogenous B2M expression abrogates age-related cognitive decline and enhances neurogenesis in aged mice. Our data indicate that systemic B2M accumulation in aging blood promotes age-related cognitive dysfunction and impairs neurogenesis, in part via MHC I, suggesting that B2M may be targeted therapeutically in old age.